A novel germline mutation of PDGFR- might be associated with clinical response of colorectal cancer to regorafenib

Rechsteiner, M ; Wild, P ; Kiessling, M K ; Bohnert, A ; Zhong, Q ; Stahel, R A ; Moch, H ; Curioni-Fontecedro, A

DOI: https://doi.org/10.1093/annonc/mdu471

Annals of Oncology Advance Access published October 20, 2014

A novel germline mutation of PDGFR-β might be associated with clinical response of colorectal cancer to regorafenib.

M. Rechsteiner[1,3], P. Wild[1,3], M.K. Kiessling[2], A. Bohnert[1], Q. Zhong[1], R.A. Stahel[2], H. Moch[1], A. Curioni-Fontecedro[2]

[1]Institute of Surgical Pathology, University Hospital Zurich

[2]Department of Oncology, University Hospital Zurich

Corresponding author: Alessandra Curioni-Fontecedro (e-mail: alessandra.curioni@usz.ch)

[3]equal contribution

We report an extraordinary response to regorafenib in a patient with metastatic adenocarcinoma of the rectum. In order to identify the molecular target of this response, we analysed 409 cancer genes by next generation sequencing of the genomic DNA (patient tumor and blood) and discovered a germline mutation of the PDGFR-β gene, a target of regorafenib. The patient (male, Caucasian) was diagnosed with rectal cancer at the age of 37 years; the initial stage was pT3pN0cM0. The patient underwent initially a rectal resection and adjuvant chemotherapy. Seven years later, recurrence of disease with metastases was diagnosed. Molecular analysis of the tumor demonstrated a *KRAS* wildtype genotype. The patient underwent multiple systemic treatments over five years. At this time the patient became symptomatic with pain and cough due to bone and lung metastases (Fig.1a). Treatment with regorafenib was initiated. After eight weeks, a PET/CT scan showed a partial morphological and metabolic response (Fig. 1b) according to RECIST criteria. After 9 months from beginning of this therapy the patient is still in partial remission with significant improvement of the symptoms (Fig. 1c). Regorafenib inhibits the angiogenic and stromal receptor tyrosine kinases (RTKs), vascular endothelial growth factors receptors (VEGFRs), tyrosine kinase endothelial 2 (TIE2) and platelet derived growth factor receptor β (PDGFR-β). In colorectal cancer patients, objective responses to regorafenib have been rarely observed (1% response rate [1]). As our patient showed a response lasting over 9 months, we analysed the patient's tumor by next generation sequencing (NGS) using targeted amplification with the AmpliSeq [2] Comprehensive Cancer panel (CCP; Ion Torrent, Life Technologies) which includes all exons of 409 cancer genes; the amplified regions were sequenced according to [3]. Alignment, variant calling, and filtering were done with Ion Reporter v4.0 (Life Technologies) and are summarized in supplementary Table 1 and 2. We detected a non-synonymous point mutation of PDGFR-β at codon 6 (p.A6V) which was confirmed by Sanger sequencing (Fig. 2a). This mutation has already been described in the COSMIC database (ID=1435169) as a unique case out of 367 colon carcinomas investigated. As this represents a rare mutation, we sequenced this region in the genomic DNA derived from the patient's peripheral blood mononuclear cells (PBMCs) and detected the same strong heterozygous signal, demonstrating this to be a germline mutation (Fig. 2b). Moreover, we could exclude the presence of this mutation in the genomic DNA derived from tumor samples of four patients affected by metastatic colorectal cancer not responding to regorafenib (Fig. 2c). A strong and homogenous expression of PDGFR-β could be detected in the patient's tumor compared to the non-responder patients (Supplementary Fig. 1). PDGF and their receptors (PDGFR-α, PDGFR-β and PDGFR-αβ) play a critical role in cancer development [4, 5]. Mutations involving up-regulation of PDGF and/or PDGFR have been documented in a number of solid tumors and hematological malignancies. In colon cancer, previous reports have shown sensitivity of a cell line with mutation (p.T681I) of PDGFR-β, to sorafenib [6] and a recent case report described another germline

mutation in exon 19 of PDGFR-β [7] associated with increased pathway activation and survival. To date, mutations of PDGFR-β have not been correlated to response to regorafenib, neither in cell lines nor in patients. Here we describe for the first time the germline mutation c.17C>T (NM_002609.3) of PDGFR-β, a target of regorafenib and hypothesize that this mutation, in the signal peptide of PDGFR-β, might have an oncogenic driver potential [8]. Although objective responders to regorafenib are rare, it would be of major interest to confirm this result in a larger group of patients to define if PDGFR-β is a predictive marker to this treatment.

The authors declare no conflicts of interest.

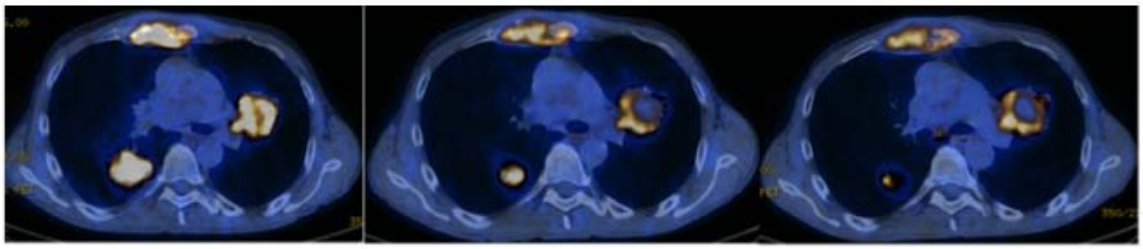
1. Grothey A, Van Cutsem E, Sobrero A et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013; 381: 303-312.
2. Tsongalis GJ, Peterson JD, de Abreu FB et al. Routine use of the Ion Torrent AmpliSeq Cancer Hotspot Panel for identification of clinically actionable somatic mutations. Clin Chem Lab Med 2013; 1-8.
3. Boland JF, Chung CC, Roberson D et al. The new sequencer on the block: comparison of Life Technology's Proton sequencer to an Illumina HiSeq for whole-exome sequencing. Hum Genet 2013; 132: 1153-1163.
4. Hoch RV, Soriano P. Roles of PDGF in animal development. Development 2003; 130: 4769-4784.
5. Yu J, Ustach C, Kim HR. Platelet-derived growth factor signaling and human cancer. J Biochem Mol Biol 2003; 36: 49-59.
6. Guida T, Anaganti S, Provitera L et al. Sorafenib inhibits imatinib-resistant KIT and platelet-derived growth factor receptor beta gatekeeper mutants. Clin Cancer Res 2007; 13: 3363-3369.
7. Estevez-Garcia P, Castano A, Martin AC et al. PDGFRalpha/beta and VEGFR2 polymorphisms in colorectal cancer: incidence and implications in clinical outcome. BMC Cancer 2012; 12: 514.
8. Martoglio B, Dobberstein B. Signal sequences: more than just greasy peptides. Trends Cell Biol 1998; 8: 410-415.

Legend to Figures and tables

Figure 1. PET-CT scans at baseline (a), after 8 weeks of treatment (b), after 5 months of treatment (c).

Figure 2: Sanger sequencing of PDGFR- β. a) To verify the variant in PDGFR-β which was detected by NGS in the responder to regorafenib, the same DNA derived from tumor tissue as used for NGS was amplified for the region of interest and sequenced by Sanger sequencing. The variant p.A6V was successfully verified. b) To investigate whether the verified mutation in PDGFR-β is tumor specific, DNA was isolated from PBMCs (blood) from the responder to regorafenib and sequenced by Sanger sequencing. The variant p.A6V was detected in PBMCs as well and thus defined as germline mutation. c) To analyse whether the germline mutation p.A6V in PDGFR-β may be a private mutation in the responder to regorafenib, tumor samples of four additional colon carcinoma patients which did not respond to regorafenib treatment were sequenced for the specific mutation in PDGFR-β. None of the non-responders to regorafenib exhibited the mutation p.A6V.

Figure 1



a b c

Figure 2